REMARKS

Claims 49, 55-73 are pending and under examination in the above-identified application. Claims 1-48 and 50-54 have been canceled. Claims 49, 55, 59, 60, 68, 69, 72 and 73 have been amended. Support for the amendments can be found throughout the application as filed. Specifically, support for the amendments to claim 49 is found in paragraphs [0032], [0296] and [0332]; support for the amendments to claim 55 is found in paragraphs [0032], [0180] [0289] and [0290]; support for the amendment to claim 60 is found in paragraphs [0175] and [0332]; support for the amendments to claim 68 is found in paragraphs [0084], [0085] and [0175]; support for the amendments to claim 69 is found in paragraphs [0064] and [0332]; support for the amendments to claim 72 is found in paragraphs [0175] and [0332]; and support for the amendment to claim 73 is found in paragraph [0332]. Claim 59 has been amended to provide proper antecedent bases of all the claim elements. The phrase "normal control" has been replaced with the phrase "control sample." Support for the amendment to claim 59 can be found in paragraph [0302]. Accordingly, the amendments do not introduce new matter and entry thereof is respectfully requested.

Objections to the Specification

The Office advises that the Abstract should reflect the elected invention. In accordance with the suggestion of the Office, Applicants have amended the Abstract to more accurately reflect the elected invention.

The Office has objected to the specification for not identifying the U.S. Application Serial Number from which the present application claims priority. In accordance with the suggestion of the Office, the specification has been amended to identify the U.S. Application Serial Number from which the present application claims priority. Applicants also respectfully direct the Office to the Supplemental Application Data Sheet submitted on September 13, 2004 by Fax with a Request for Corrected Filing Receipt. The Supplemental Application Data Sheet provided the domestic priority information as stating that the above-identified application is a continuation-in-part of 10/691,209 filed on 10/21/2003. Applicants further provided as Exhibit A, the first page of the Transmittal of New Application of U.S. Application Serial Number

10/691,209 filed on 10/21/2003, which identifies the Attorney docket no. as 529452002400. As such, Applicants submit this is sufficient evidence to perfect the priority claim.

The Office has objected to the specification for failing to comply with the Sequence Rules as set forth in the 37 C.F.R. 1.821-1.825. Specifically, the sequence "WSXWS" is not accompanied by a SEQ ID Number. In accordance with the suggestion of the Office, the specification has been amended to identify a corresponding SEQ ID Number for the identified sequence. A Replacement Sequence Listing is being provided herewith in computer readable form "CRF" on a compact disc, with two additional copies marked "Copy 1" and "Copy 2." A Statement is provided herein to support filing and submission in accordance with 37 C.F.R §§ 1.821-1.825.

Rejections Under 35 U.S.C. 112, Second Paragraph

Claims 49 and 55-73 stand rejected under 35 U.S.C. 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 49 stands rejected for omitting what the first tissue type is or whether or not the first individual is suffering or suspected of having cancer. Claim 49 also stands rejected for failing to clearly limit what the first individual is affected with. While believed to be clear as written, claim 49 now recites the claim element "determining the expression of a cytochrome B5 gene in a suitable tissue sample from a first individual suspected of being affected with cancer," which is supported by the disclosure of the subject application. Specifically, Applicants direct the Office to paragraphs [0032], [0043] and [0282].

Claims 55, and by way of their dependence claims 56-59, stand rejected for the use of the term "normal control," which is allegedly unclear. While believed to be clear as written, claim 55 now recites the claim element "normal non-cancerous control sample" which is supported by the disclosure of the subject application. Specifically, Application direct the Office to paragraphs [0282], [0303] and [0332].

Claim 60, and by way of their dependence claims 61 and 65-67, stand rejected for allegedly failing to recite a final process step which agrees back with the preamble. Specifically,

the Office asserts that claim 60 is drawn to a method of diagnosing cancer, yet the claim recites only an active step of comparing the expression level of cytochrome B5 gene between two samples. The Office also rejects claims 49, and 55-73 as being allegedly indefinite analogously. Applicants respectfully traverse the rejection.

Applicants submit that the correlation of the genes and sequences identified in claims 49, 55-73, such as cytochrome B5 or SEQ ID NO:869 are identified throughout the subject application as being correlated with a diagnosis of cancer, including colon, breast, prostate and stomach cancer. Claim 49 includes two steps: determining the expression of cytochrome B5 in a first sample and comparing the expression of cytochrome B5 from the first sample to a second sample. Claim 55 and all dependent claims thereof include two steps: determining the level of cytochrome B5 mRNA is a patient sample and comparing the level of mRNA in the patient sample to a control sample. Each claim includes at least one process step and correlates back to the preamble of each claim by reciting what claim elements indicates the individual has or is predisposed to have cancer or a specific type of cancer.

Claim 60 stands rejected for being indefinite as allegedly the claim recites that a differential expression of cytochrome B5 is detected, but allegedly fails to recited to what the cytochrome B5 of level from a patient sample is being compared against. Applicant's have amended claim 60 to recite "as compared to a normal non-cancerous control sample."

Claims 61, and 65-67 stand rejected for being dependent on claim 60. Applicants respectfully direct the office to the amendment of claim 60 above.

Claim 68 stands rejected for being indefinite for reciting the phrase "highly stringent conditions." The Office asserts that without a specific definition in the specification which limits the term, "highly stringent condition" to a particular set of conditions, one of skill in the art would not know when the conditions will stop being low, moderate, or high. Applicants respectfully traverse the rejection. The specification of at paragraphs [0084] and [0085] define highly stringent conditions. Specifically, in one example suitable highly stringent hybridization conditions include those described in paragraph [0084] with the exception that the temperature of hybridization is increased, e.g., to 60-65°C, or 65-70°C. Furthermore, Applicants have amended claim 68 to recite, "wherein said polynucleotide hybridizes under highly stringent binding

conditions to a nucleotide sequence comprising SEQ ID NO:869 and said highly stringent binding conditions comprise hybridization at 60-65°C in 5 X SSC (9 mM saline /0.9 mM sodium citrate)."

Claim 68 also stands rejected for being indefinite because the limitation defining the hybridization found on the last line of the claim is allegedly ambiguous as to which hybridization it is referencing. Applicants have amended claim 68 to more clearly identify which hybridization is being referenced. Step (a) of claim 68 now recites "contacting a polynucleotide with nucleic acids of a patient colon, breast or prostate sample under conditions suitable to form a duplex, wherein said polynucleotide hybridizes under highly stringent binding conditions to a nucleotide sequence comprising SEQ ID NO:869 and said highly stringent binding conditions comprise hybridization at 60-65°C in 5 X SSC (9 mM saline /0.9 mM sodium citrate)."

Claim 69 stands rejected for being indefinite for the recitation of the phrase "control." It is allegedly unclear what is deemed a "control." Applicants have amended claim 69 to recite the claim element "a normal non-cancerous control sample."

Claim 70 and 71 stand rejected for being dependent on claim 69. Applicants respectfully direct the office to the amendment of claim 69 above.

Claim 72 stands rejected for being indefinite for the recitation of the phrase "control colon sample." Applicants have amended claim 72 to recite the claim element "a normal non-cancerous control colon, stomach, or prostate tissue sample."

In light of the amendments and arguments presented above, Applicants respectfully request withdrawal of all of the above rejections.

Rejections Under 35 U.S.C. 112, First Paragraph – New Matter

Claims 49 and 55-67 stand rejected under 35 U.S.C. 112, first paragraph for allegedly having new matter. The Office alleges that the claims as originally filed do not disclose that SEQ ID NO: 869 as being cytochrome B5 gene and the specification as originally filed does not contain this characterization. Applicants respectfully traverse the rejection.

SEQ ID NO: 869 is identified as the human mRNA sequence of cytochrome B5 in Table 93 of the CD-ROM submitted with the application on October 22, 2003. Paragraphs [0002] and [0003] identify that Tables 1-336 are filed in CD-ROM in accordance with 37 C.F.R. §§ 1.52 and 1.58 and incorporates by reference into the specification their contents. A portion of Table 93 is provided in Exhibit B for ease of reference. Applicants respectfully submit that the specification as originally filed supports the recitation of cytochrome B5 in claims 49 and 55-67. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S.C. 112, First Paragraph – Written Description

Claims 49, 55-70 and 73 stand rejected under 35 U.S.C. 112, first paragraph for allegedly lacking written description. The Office alleges that the specification fails to provide a sufficient description of a representative number of species by 1) reduction to practice; 2) reduction to drawings; or 3) disclosure of relevant identifying characteristics. Applicants respectfully traverse.

Applicants submit that the specification provides sufficient support to satisfy the written description requirement under section 112, first paragraph. For example, since cytochrome B5 and specifically SEQ ID NO:869 is identified as being a CA polypeptide in Table 93 (a portion provided as Exhibit B), the descriptions for the methods of identifying homologues of the CA polypeptide and encoding nucleic acid sequences provided in paragraphs [0077] through [0087], the variants of the CA polypeptides provided in paragraphs [0122] through [0134], and methods of making such variants of the CA polypeptides provided in paragraphs [0135] through [0146] provides disclosure of relevant identifying characteristics of cytochrome B5 and SEQ ID NO:869. Specifically, the specification in paragraph [0134] states:

> The variants typically exhibit the same qualitative biological activity and will elicit the same immune response as the naturally-occurring analogue, although variants also are selected to modify the characteristics of the CA proteins as needed. Alternatively, the variant may be designed such that the biological activity of the CA protein is altered. For example, glycosylation sites may be altered or removed, dominant negative mutations created, etc.

Therefore, by describing the variants of the polypeptides, and that they can be made by changing the encoding nucleic acid, the application describes variants of the encoding nucleic acid. The

variants fall into substitutions, insertions and deletions that can be prepared from mutagenesis of the encoding nucleic acid. Moreover, as described therein, the variants typically exhibit the same qualitative biological activity as the naturally occurring sequence.

This description of a number of variants of CA polypeptide and encoding nucleic acid sequences is sufficient to satisfy the representative number of species articulated by the Office. Further, this description adequately describes the claimed invention such that one skilled in the art can recognize what is claimed. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S.C. 112, First Paragraph – Enablement

Claim 49 and 55-73 stand rejected under 35 U.S.C. 112, first paragraph for allegedly lacking enablement. The Office asserts that the question of enablement is risen because the application has no data to support this general hypothesis that simply because there is a "strong likelihood" of an oncogene, which is involved in leukemia, being involved in other types of cancers, one of skill in the art would accept without question that any nucleic acid sequence involved in leukemia can be employed for diagnosis of other types of cancers. The Office cites the seven factors of *In re Wands*, 858 F. 2d 731 (Fed. Cir. 1988). Applicants respectfully traverse the grounds of this rejection for the following reasons.

Enablement does not require absolute predictability. Rather, requires that a person skilled in the art be able to practice the invention without undue experimentation. *In re Wands,* at 737 & 738. Factors to be considered in determining whether undue experimentation would be required to practice an invention included (1) the nature of the claimed invention, (2) the breadth of the claims, (3) the relative skill in the art, (4) the state of the prior art, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary to make or use the invention, (7) the amount of direction or guidance presented in the application, and (8) the predictability or unpredictability of the art. *Id.* No one factor is determinative, and the enablement requirement is met if a preponderance of the evidence indicates that it is more likely than not that any person skilled in the art at the time the application was filed could have practiced the claimed methods directed to diagnosing cancer or more specifically colon, breast, stomach or prostate cancer by comparing the expression of the recited cytochrome B5 encoding

nucleic acids first in a patient sample or a sample form an individual suspected of being affected with cancer to a normal non-cancerous control sample as claimed without undue experimentation. Applying the factors enumerated in *In re Wands* demonstrates that claims 49 and 55-73 are enabled and that undue experimentation would not be required to make and use the invention as claimed.

Factors 1 and 2: The nature of the claimed invention and breadth of the claims.

Claims 49 and 55-73 are directed to methods for diagnosing cancer or more specifically colon, breast, stomach or prostate cancer by determining the difference in expression of a cytochrome B5 gene or more specifically a cytochrome B5 encoding nucleic acid (SEQ ID NO:869) in colon, breast, stomach or prostate cancer tissue compared to a normal non-cancerous tissue sample.

As taught by the specification, the use of oncogenic retroviruses –whose sequences insert into the genome of the host organism and result in cancer– has allowed the identification of host cancer related sequences such as cytochrome B5, defined as a cancer associated (CA) gene or nucleic acid sequence. See the specification at paragraphs [0040], [0041], [0062] and Table 93 (a portion of which is provided as Exhibit B). In this regard, the specification teaches the use of three mammalian retroviruses (i.e., FeLV, MLV and MMTV) for tagging and identifying protooncogenes. See paragraph [0040]. The specification describes that the integration of provirus affects the expression of host genes at or near the site of integration. See paragraph [0040]. Possible changes in the expression of host cell genes due to insertional mutagenesis are taught to include: (i) increased expression of genes near the site of integration resulting from the proximity of elements in the provirus that act as transcriptional promoters and enhancers, (ii) functional inactivation of a gene caused by the integration of a provirus into the gene itself thus preventing the synthesis of a functional gene product, or (iii) expression of a mutated protein that has a different activity to the normal protein. See paragraphs [0062] and [0064] to [0066].

The specification also teaches that differential expression of the CA genes such as cytochrome B5 can be used for diagnosis of cancer or detection of cancer phenotype. See paragraph [0175]. As will be discussed below, the specification further provides information about various means by which the differential expression of CA genes (including their mRNAs

and proteins) can be determined. See paragraphs [0175], and [0284] through [0295]. Thus, the present specification teaches that the differential expression of cytochrome B5 or the cytochrome B5 encoding nucleic acids comprising SEQ ID NO:869 can be used as claimed for diagnosis of cancer.

Factors 3 and 4: The relative skill in the art and the state of the prior art.

The Office contends that the art of cancer diagnosis is unpredictable, and that Tockman (Tockman, M.S. et al. Cancer Research, (Suppl.) 57:2711s-2718s, 1992) discloses that research must validate the markers against acknowledged disease end points and confirm marker predictive value. The Office also contends that Lecentini et al. and Wacholder et al. share the importance of exercising caution when implicating a biomarker with a particular disease. Applicants respectfully traverse.

Applicants submit that the specification teaches one skilled in the art that the claimed sequences are sufficient to be predictive of cancer or more specifically colon, breast, stomach or prostate cancer. As described above, the specification discloses that cytochrome B5 encoding nucleic acid sequences SEQ ID NO:869 was discovered through the retroviral insertional mutagenesis as a marker for diagnosis of cancer. The specification teaches that the product of a CA gene such as cytochrome B5 can be a marker for cancer diagnosis, when the gene expression is differentially altered in a tissue as compared to a control such as normal non-cancerous colon, stomach or prostate tissue or such tissue isolated from an unaffected individual. See paragraphs [0032] and [0156]. The end point for which the cytochrome B5 is to be a marker is measured, according to the specification, by differential expression that is defined and quantified in terms of up- or down-regulation. See paragraphs [0062] and [0064] to [0066]. The specification further establishes the range of cytochrome B5 gene product variability in terms of, for example, sequence homology (of least 95% to cytochrome B5 mRNA) or hybridization at highly stringent condition (of e.g., 60-65° C in 5X SSC). See paragraph [0077] and [0084]. The specification further describes means for determining sequence homology in paragraphs [0077] through [0087] and provides detail disclosure for hybridization conditions in paragraphs [0084] through [0085]. The specification also provides information about the biological samples which can be used for detecting the CA gene expression and diagnosing cancer. See paragraph [0303]. The

specification teaches that, for example, laser capture microdissection can be used to obtain samples from tumor and normal tissues. See paragraph [0322].

The present specification and the state of the prior art at the time the application was filed indicate that the relative skill in the art in relation to the subject matter to which the claimed invention pertains was high. At that time the application was filed, it was routine for a person skilled in the art to use recombinant DNA methods to determine the differential expression of, for example, cytochrome B5 nucleic acids or products comprising or encoded by SEQ ID NO:869 or a nucleic acid sequence with at least 95% or alternatively at least 98% homology with SEQ ID NO: 869 or cytochrome B5 protein in tissue samples.

As provided in the specification, it was also routine for one skilled in the art to be able to test cytochrome B5 nucleic acids or their products for diagnosing cancer. Various means for detection of CA gene's nucleic acid product expression are disclosed in the specification at paragraphs [0320] through [0330]. Various means for detection of CA gene's encoded protein expression are disclosed in the specification at paragraphs [0340] through [0342] and [0349] through [0354]. Thus the specification not only taught that cytochrome B5 nucleic acids and expression products can be used to diagnosing cancer; but it also provided detailed support for a skilled artisan to carry out the claimed methods for diagnosing cancer.

Factor 5: The presence of working examples.

The Office contends that there are no working examples for the method of diagnosing colon cancer by differential expression detection of cytochrome B5 or the polynucleotide of SEQ ID NO:869 or its homologous sequences. Applicants respectfully traverse.

The MPEP, Section 2164.02, states: "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation."

The specification in Example 2, paragraphs [0316] through [0319], provides an example in which the RT-PCR method can be used for analysis of differentially expressed gene. See also Figures 2-4. In paragraph [0320], the specification provides an example of detection of elevated

levels of cDNAs associated with cancer (e.g., cytochrome B5 cDNA) using arrays. Methods for detection of CA sequences (e.g., cytochrome B5 gene) in human cancer cells and tissues by way of hybridization are taught in Example 4, paragraphs [0332] through [0334]. Furthermore, generation of antibodies against CA polypeptides (e.g., cytochrome B5 gene polypeptide) is taught in Examples 6-7, paragraph [0337] through [0339]. Various methods for detection of CA proteins (e.g., cytochrome B5 gene protein) have also been taught in Examples 8-9, paragraphs [0340] through [0342].

The specification also teaches that "[c]omparing expression patterns of uncharacterized genes may provide clues to their function. High throughput analysis of expression of hundreds or thousands of genes can help in (a) identification of complex genetic diseases, (b) analysis of differential gene expression over time, between tissues and disease states, and (c) drug discovery and toxicology studies. Increase or decrease in the levels of expression of certain genes correlate with cancer biology. For example, oncogenes are positive regulators of tumorigenesis, while tumor suppressor genes are negative regulators of tumorigenesis. (Marshall, Cell, 64: 313-326 (1991); Weinberg, Science, 254: 1138-1146 (1991))." See paragraph [0008]. The specification also provides means for detection of cancer profile and correlating the expression levels of CA genes (e.g., cytochrome B5) to the cancer phenotype. See paragraphs [0174] through [0188].

Therefore, in view of the extensive teachings and exemplifications provided in the specification, a skilled artisan could have reasonably correlated the *in vitro* effects of the claimed methods to their *in vivo* utility in providing means for diagnosing cancers.

Factors 6 and 7: The quantity of experimentation necessary to make or use the invention and the amount of direction or guidance presented in the application.

The person of ordinary skill in the art would be able to practice the claimed invention following the guidance of the specification, using no more than routine experimentation. Cytochrome B5 nucleic acids and techniques suitable for detecting their differential expression in a patient tissue sample and comparing it to a normal control such as non-cancerous colon, stomach or prostate tissue sample were known in the art at the time the application was filed. The specification further provides detail information for a skilled person to carry out the claimed method. See the information provided in Example 2 for analysis of quantitative RT-PCR:

comparative C_T method; Example 3 for detection of elevated levels of cDNA associated with cancer using arrays; Example 4 for detection of CA-sequences in human cancer cells and tissues; Example 5 for expression of cloned polynucleotide in host cells; Example 6 for generation of antibodies against polypeptides; Example 7 for generation of monoclonal antibodies against a CA polypeptide; Example 8 for ELISA assay for detecting CA related antigens; Example 9 for identification and characterization of CA antigen on cancer cell surface; Example 12 for diagnostic imaging using CA specific antibodies; and Example 13 for immunohistochemical methods disclosed.

Thus, the specification teaches the person of skilled in the art that differential expression of CA genes (including cytochrome B5 gene) and their products for diagnosing cancers are reliable and that detection of the differential expression leads to diagnosis of cancer. Accordingly, the specification provides ample guidance regarding the structure-function of cytochrome B5 expression to enable any person skilled in the art to make or use the claimed methods without undue experimentation.

Factor 8: The predictability or unpredictability of the art.

The Office alleges that the instant invention, as claimed, falls under the "germ of an idea" concept and that enablement cannot be established unless one skilled in the art "would accept without question" an Applicant's statements regarding an invention. Applicants respectfully traverse.

Applicants submit that the present invention represents more than a mere germ of an idea, the specification supplies the novel aspects of the invention, i.e. that cytochrome B5 is a cancer-associated gene, and identification of the necessary elements which enable the skilled artisan in practicing the claimed invention, as described in detail above. See *Genentech, Inc. v. Novo Nordisk*, 42 U.S.P.Q.2d 101, 108 F.3d 1361 (Fed. Cir. 1997).

While such procedures involve some level of technical manipulation, because such methods and steps are routinely used in the art, the procedures do not rise to the level of undue experimentation. See *Johns Hopkins University v. Cellpro, Inc.*, 47 U.S.P.Q.2d 1705, 152 F.3d

1342 (Fed. Cir. 1998), where the court stated that experimentation does not constitute undue experimentation where it is merely routine.

Furthermore, Applicants submit that the specification contains a teaching of the manner and process of making and using the invention, as described in detail above, and that the Office has provided no reason to doubt the objective truth of the statements contained therein. See *Rasmusson v. SmithKline Beecham Corp.*, 75 U.S.P.Q.2d 1297, 413 F.3d 1318 (CAFC 2005), where the court states a specification disclosure which contains a teaching of the manner and process of making and using the invention ...must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In view of the foregoing arguments, Applicant submit that claims 49, 55-73 are enabled because, in view of state of art, teachings and exemplifications provided in the application, a person of ordinary skill in the art could make or use the claimed methods without undue experimentation. Accordingly, Applicant respectfully request withdrawal of this rejection.

CONCLUSION

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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